Summary Minutes of the
Cardiovascular and Renal Drugs Advisory Committee
July 29, 2009

Location: Hilton Washington DC/Silver Spring, Maryland Ballroom,
8727 Colesville Road, Silver Spring, MD.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

These summary minutes for the July 29, 2009 Meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on September 4, 2009.

I certify that I attended the July 29, 2009 meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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Elaine Ferguson, M.S.,R.Ph.
Designated Federal Official

Robert Harrington, M.D. F.A.C.C.
Committee Chair

Meeting of the Cardiovascular and Renal Drugs Advisory Committee
July 29, 2009

The following is an internal report which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm125999.htm

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The Cardiovascular and Renal Drugs Advisory Committee, Center for Drug Evaluation and Research met on July 29, 2009 at the Hilton Washington DC/Silver Spring, Maryland Ballroom, 8727 Colesville Road, Silver Spring, MD. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. This was a voting meeting. There were approximately forty (40) persons in attendance.

Issue: The committee discussed supplemental new drug application (sNDA) 20–850/S–025, telmisartan tablets, 80 milligrams, Boehringer Ingelheim Pharmaceuticals, Inc., for the proposed indication of reduction in the risk of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for congestive heart failure in patients 55 years or older who are at high risk of developing major cardiovascular events.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):

Robert A. Harrington, M.D., F.A.C.C. (Chair), Sanjay Kaul, M.D. , Mori J. Krantz, M.D., F.A.C.C., Emil P. Paganini, M.D., F.A.C.P., F.R.C.P.,

Special Government Employee Consultants (Voting):

Ralph B. D'Agostino, Ph.D., David DeMets, Ph.D., Sidney M. Wolfe, M.D.

Industry Representative Member Present (Non-Voting):

Jonathan C. Fox, MD, PhD, FACC

Guest Speaker (Non-Voting): None

FDA Participants (Non-Voting):

Robert Temple, M.D., Norman Stockbridge, M.D., Robert O'Neill, Ph.D.

Designated Federal Official:

Elaine Ferguson

Open Public Hearing Speaker:

James Baranski CEO, National Stroke Association

The agenda was as follows:

8:00 a.m.	Call to Order Introduction of Committee	Robert A. Harrington, M.D. Chair, CRDAC
	Conflict of Interest Statement FDA	Elaine Ferguson, M.S. Designated Federal Official, CRDAC
8:05 a.m.	Opening Remarks	Norman Stockbridge, M.D. Director, Cardiovascular and Renal Drug Products, CDER
8:10 a.m.	Sponsor Presentations: Introduction	Thor Voigt, MD. Senior VP of Medicine & DRA, Boehringer Ingelheim Pharmaceuticals, Inc.
	Clinical Need	James Young, MD. Executive Dean, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
	Efficacy	Salim Yusuf, DPhil, FRCPC, FRSC. Prof. of Medicine (McMaster University) and Director, PHRI, VP Research & CSO, Hamilton Health Sciences, Heart & Stroke Foundation Endowed Chair in CV Research
	Safety	Jeffrey Friedman, MD Therapeutic Area Head Cardiovascular, Boehringer Ingelheim Pharmaceuticals, Inc.
	Risk / Benefit and Conclusions	James Young, MD. Executive Dean, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
9:40 a.m.	Questions to the Sponsor	
10:10 a.m.	Break	
10:25 a.m.	Clinical and Statistical Review of NDA 20-850/S-025 (Micardis)	Khin Maung U, M.D. Clinical Reviewer, Division of Cardiovascular and Renal Products, FDA Jialu Zhang, Ph.D. Statistical Reviewer, Division of Biometrics I, FDA
10:55 a.m.	Questions to the presenters	
Noon	Lunch	
1:00 p.m.	Open Public Hearing	
2:00 p.m.	Discussion of questions to committee	
3:30 p.m.	Break	
3:45 p.m.	Discussion of questions to committee	
5:00 p.m.	Adjourn	

Questions to the Committee

Please refer to the transcript for additional comments and detail.

1. In HOPE, ramipril was associated with a 22% relative risk reduction in the primary end point of cardiovascular death, myocardial infarction, or stroke. This finding included a 26% relative risk reduction (2.0% absolute) in cardiovascular death, a 20% relative risk reduction (2.4% absolute) in myocardial infarction, and a 32% relative risk reduction in stroke (1.5% absolute). There was a relative risk reduction of 16% (1.8% absolute) for all-cause mortality.

   1.1 In comparing a new treatment to ramipril, is it sufficient to ensure that the new treatment would likely have been superior to placebo? On what endpoint?

   The Committee generally agreed that compelling evidence of effectiveness sufficed. Given the non-inferiority basis, having appropriate adjustments for variable outcomes and for temporal trends was considered to be important. Some Committee members were uncomfortable with HOPE being the sole basis for estimating the effect of ramipril in ONTARGET, as later studies with other drugs showed smaller effects.

   The committee was ok with a composite endpoint; however, the components need to be clinically significant, not subjective (such as hospitalization). Many of the committee members wanted to see consistency in the results across the components.

   1.2 If not, what proportion of this benefit is it appropriate to ensure has been preserved? On what endpoint?

   Ensuring preservation of some fraction of the historical effect is a matter of clinical judgment. This concern has to tempered with considerations of the practicality of conducting very large trials and the need to have therapeutic alternatives.

2. In non-inferiority testing, there are various strategies intended to ensure that the new therapy would likely have been superior to placebo. How did the sponsor's strategy address …

   2.1 … use of a single reference study?

   2.2 … choice of end point from HOPE?

   2.3 … early termination of HOPE?

   2.4 … evolving treatment of high-risk patients?

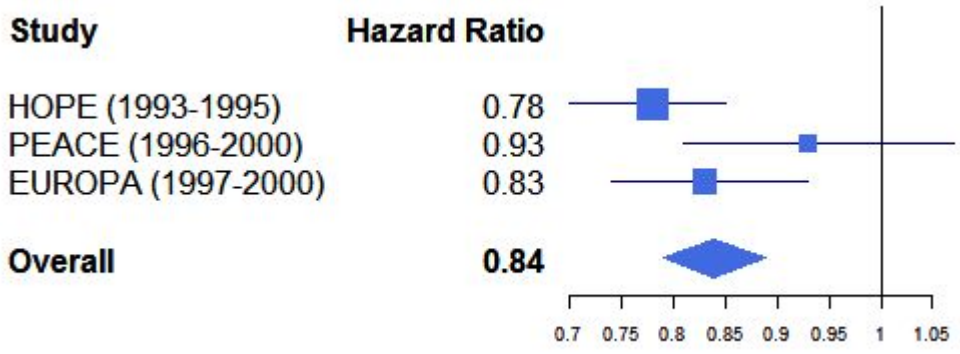
   It was ok to use HOPE only; however, a suggestion was made that the estimates of the margins should have been more conservative, there should have been more accounting for variability.

   The committee was comfortable with the early termination of HOPE given the conservative stopping rules of the trial. The P value could be adjusted statistically to account for early termination. With conservative boundaries the adjustment would be small.

   The committee members preferred the triple end point and were willing to consider it, even though it was not the primary end point.

   With the addition of CHF Hospitalization the results may reflect a change in CHF treatment, particularly the increased use of beta blockers.

3. Are EUROPA (perindopril) and PEACE (trandolapril) relevant? If so, given the results of EUROPA and PEACE, …



   3.1 … how confident are you in the constancy assumption? What discount on the expected effect of ramipril is appropriate?

It is difficult to ignore the data, so it should be considered. There is a potential explanation for PEACE being an outlier.

3.2… should a pooled analysis of ACE effect size be based upon fixed-effect or random-effect modeling?

With a small number of trials the statisticians felt more comfortable with, and thought it to be preferable to use, fixed-effects modeling.

4 What should the non-inferiority margin be?

The committee accepted the FDA's argument for determining the non-inferiority margin. It was suggested that perhaps feasibility should have been considered and a compromise made. The committee wanted clinical significance to be incorporated.

5 What role do the following observations play in your consideration of the effectiveness of telmisartan for reducing cardiovascular events?

5.1 The lack of superiority of the combination of telmisartan and ramipril to ramipril alone in ONTARGET (HR 0.99; 95% CI 0.92-1.07; p=0.85).

5.2 The lack of effect on the 4-component primary end point in TRANSCEND, a placebo-controlled study in high-risk ACE-intolerant patients (HR 0.92; 95% CI 0.81-1.05; p=0.22).

5.3 The favorable trend on the 3-component endpoint in TRANSCEND (HR 0.87; 95% CI 0.76-1.00; p=0.049).

5.4 The lack of effect seen in PRoFESS, a placebo-controlled study in patients with a prior stroke (HR 0.94[1]; 95% CI 0.83-1.01; p=0.11).

You cannot ignore the primary event. Collectively all these things say… be cautious.

6 Voting questions:

6a. Should telmisartan be approved to reduce cardiovascular events in patients at high risk for such events?

Yes = 0

No = 7

6b. If you voted no, should telmisartan be approved to reduce cardiovascular events in patients at high risk for such events and who can not tolerate ramipri**l**

Yes = 5

No = 2

After voting, please comment on the rationale for your vote.

6a. The committee members expressed that the data were not strong enough to support an unrestricted approval, since the data were not convincing that telmisartan preserved most of the expected effectiveness of ramipril..

6b. The committee members who voted yes considered the unmet need among patients who are intolerant of ACE inhibitors in addition to their judgment that a reduction in risk was well established. The members who voted no questioned the certainty of the treatment effect, within the changing landscape of treatments for cardiovascular death.

[1] This is for the 4-fold cardiovascular composite end point, not for the primary end point, which was stroke.